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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,984	01/04/2002	Yin-Xiong Li	275.0003 0102	9705

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,984	LI ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7, 9, 10, 15-25, 27-32, 39, 48 and 61-80* is/are pending in the application.

4a) Of the above claim(s) *61 and 64-67* is/are withdrawn from consideration.

5)☒ Claim(s) *75 and 76* is/are allowed.

6)☒ Claim(s) *1-7,9,10,15-20,22-25,27-32,39,48,62,63,68-74 and 77-80* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the application

Claims 1-7, 9, 10, 15-25, 27-32, 39, 48, 62, 63 and 68-74 have been examined. Claims 61 and 64-67 are withdrawn from further consideration. New claims 75-80 have been added and are examined.

Response to Arguments-Specification

The amendment filed April 28, 2003 is maintained as objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant's arguments have been considered but are not persuasive. The portions of the specification pointed to by Applicants as referring to murine cells and rat cells are directed to general contemplations of what the invention encompasses, while the amendment changes the teachings of work actually performed by the inventors. The original disclosure refers to a specific cell line known to those in the art as a mouse cell line. The amendment attempts to change the recitation of this mouse cell line to be a rat cell line. Regardless of whether the error was inadvertent, change of a mouse cell line to a rat cell line constitutes new matter. Applicants have further asked for a legal basis for requiring factual evidence of inadvertent error. The original objection was not stating that factual evidence is required, but simply noting that the declaration did not provide evidence, only assertion.

Claim Rejections - 35 USC § 112

The written description rejection is withdrawn.

The rejection of claim 21 as not being enabled is withdrawn. Also, the scope of the rejection of the claims being maintained as rejection has been revised. Response to Applicant's arguments can be found following the restatement of the rejection.

Claims 1-7, 9, 10, 15-20, 22-25, 27-32, 39, 48, 62, 63 and 68-74 are maintained as rejected and new claims 77-80 are rejected under 35 U.S.C. 112, first paragraph for the reasons of record, because the specification, while being enabling for a method of attenuating the expression of target genes in zebrafish cells or embryos, avian neural crest tissue explant culture and in rat [murine NIH/3T3] cell culture, does not reasonably provide enablement for attenuating the expression of any gene *in vivo* in any vertebrate cell except zebrafish embryos. Moreover, the specification does not reasonably provide enablement for a method for treating a disease or infection in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Response to Arguments Regarding Enablement

Applicants argue that the Examiner has concentrated on two of the Wands factors while improperly ignoring others. This is not the case as throughout the rejection the teachings, including working examples, of the specification are discussed and the

numerous references cited indicate the state of the art. The Examiner agrees with Applicant's statement that the level of skill in the art is high.

Applicant asserts that the specification is enabling for the genus of target genes encompassed by the claims and cites the working examples of attenuation of expression of several genes in zebrafish embryos, one endogenous gene in avian neural crest tissue and one reporter gene in murine NIH/3T3 cells. These arguments are not persuasive because the disclosure provides examples of attenuation of gene expression of three vertebrate species while the claims are directed to all vertebrate species, which number in the tens of thousands. Further, of the working examples in the specification, two of the three species were studied in cell culture while the claims as amended now read solely on in vivo embodiments. As described in the reference of Crooke, cell culture examples cannot be directly extrapolated to predict in vivo results. Applicant further states the zebrafish is a model organism for human biology. While the zebrafish may be a model organism for studies of gene function, this does not speak to the ability of zebrafish to model human gene therapy.

Applicant argues that the rejection regarding methods of treating a disease are not pertinent as the specification does not describe a method of therapy directed at a particular gene but rather a general method that is applicable to a wide variety of genes. This argument is not persuasive because claims 6, 7, 72 and 73 are specifically directed to methods of treating disease or infection.

Applicant state that the examiner has improperly relied upon post-filing date to demonstrate a lack of enablement and cites *In re Wright* to support that such references are only proper to demonstrate that one of skill would not believe the prophetic

teachings of the specification. This is the situation in the instant application. The specification discloses that the claimed method can target disease causing genes or infection and hence embraces methods of treatment. The claims are directly solely to in vivo embodiments and embrace all vertebrates. However, the specification does not provide any treatment of a disease and only one exemplified in vivo embodiment.

Applicant argues that the message of the Trends in Genetics reference by Fire is that gene silencing in lower organisms is predictable and this reference thus supports enablement of the present claims. With regard to the Nature reference by Fire, Applicants submit that one of skill would suspect that the one non-specific ds RNA described by Fire would be expected to interfere with related proteins due to the existence of a highly conserved domain and that these observations do not argue against specificity or predictability of RNA interference. This argument is not persuasive because the claims are directed to vertebrates, not lower organisms, which given the teachings of the Fire reference, would include plants, nematodes, trypanosomes, fruit flies and planaria. Also, these apparently contradictory teachings, as well as the references describing issues such as degree of attenuation, toxicity and possible immune responses provide support for the argument that the field of RNA interference is in its infancy and that several questions regarding mechanism, specificity and side effects relating to predictability remain to be determined. Applicants state they should not be required to prove the absence of toxicity or immune response when claims are directed to vertebrate cells. However, no such requirement has been made.

Applicant argues that the specification provides numerous details on delivery of dsRNA. The pages of the specification cited provide a list of possible delivery methods

that have been used for delivery of nucleic acids and cites exemplified embodiments where dsRNA is delivered by microinjection or soaking in a solution containing the dsRNA. These arguments are not persuasive because the specification provides a general teaching of possible delivery methods but does not provide specific guidance on how to predictably deliver dsRNA to specific cells of any vertebrate organism. While the exemplified embodiments are effective means to deliver dsRNA to embryos or cells in culture, they are not generally applicable to all vertebrate species.

Applicant further argues with regard to delivery that because the claim recites only "supplying the cell with a dsRNA", all that is required to enable the claims is that methods of supplying dsRNA to cells be described in the specification or known in the art and that pharmacological concerns such as metabolism and targeting to a particular location are not relevant. This is not persuasive because a claim must be enabled over its full scope and while it may possible to deliver a dsRNA into any body cavity, in order for the claimed method to work the dsRNA must enter a cell and exert a measurable effect hence pharmacological concerns such as targeting to a particular location are relevant to whether the invention can be used without undue experimentation.

Applicants assert that the references cited to describe technical difficulties with delivery of nucleic acids deal with antisense nucleic acids, which are distinct from the double stranded RNA, used for the present invention. However, with regard to delivery of nucleic acids to an organism, the differences between a single stranded DNA and a double stranded RNA are not significant and the obstacles that exist for antisense nucleic acids are equally or more important for double stranded RNAs, which are larger and have the potential of encountering greater issues with regard to uptake due to their

greater negative charge. Applicant argues that the literature contains many examples of systemic delivery of antisense and cites the review of Wang et al. that describes how to target oligonucleotides for the liver. These arguments are not persuasive as targeting to a single organ is not predictive of targeting to all organs or cells.

Applicants state that a presumption exists that an application is enabled without evidence that undue experimentation is necessary to perform the claimed invention and further states they do not believe undue experimentation would be necessary to practice the invention. Applicant states that the steps of identifying gene sequences and producing RNA that will hybridize to the target are performed with methods routine to those in the art. This may be true, but the other step asserted by applicant to be routine, such as delivery, is also routine. This is not true, the numerous references cited by the Examiner support that finding that methods of delivering nucleic acids to an organism in such a way that the nucleic acids enters the targeted cell in a sufficient concentration and for a sufficient length of time to have a measurable effect are not routine and predictable.

Claim Rejections - 35 USC § 102

The rejection of record of claims 1-10, 15-25, 28-30, 62, 63 and 68- 74 under 102(b) as being anticipated by Fire et al. is withdrawn in view of the claim amendments submitted March 8, 2005.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 77 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 77 depends from claim 1 and recites that the double stranded RNA comprises overhanging ends. No support could be found in the specification for double stranded RNA comprising overhanging ends. In fact, at page 13 the specification teaches that it is preferable to treat the dsRNA with RNase and notes this will remove overhanging ends.

> "Prior to administration, the mixture containing the annealed (i.e., double stranded) RNA is preferably treated with an enzyme that is specific for single stranded RNA (for example, RNAse A or RNAse T) to confirm annealing and to degrade any remaining single stranded RNAs. Addition of the RNAse also serves to excise any overhanging ends on the dsRNA duplexes."

Allowable Subject Matter

Claim 21 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 75 and 76 are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
June 9, 2005